

Gunnar Sartor

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**Prevention and Therapy of Diabetes Mellitus
with Diet Regulation and Sulfonylurea Drugs**



Lund 1980

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Prevention and therapy of diabetes mellitus
with diet regulation and sulfonylurea drugs

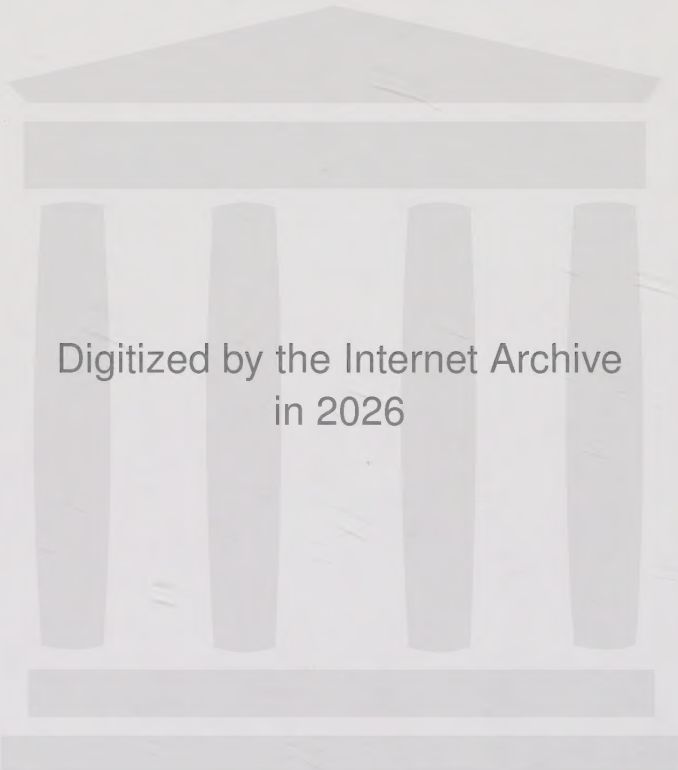
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From the Departments of Internal Medicine (Lund University Hospital) and Clinical Pharmacology (Malmö General Hospital), University of Lund, and the Department of Community Care Sciences, Dalby; Lund, Malmö, and Dalby, Sweden.

Gunnar Sartor

Prevention and therapy of diabetes mellitus with diet
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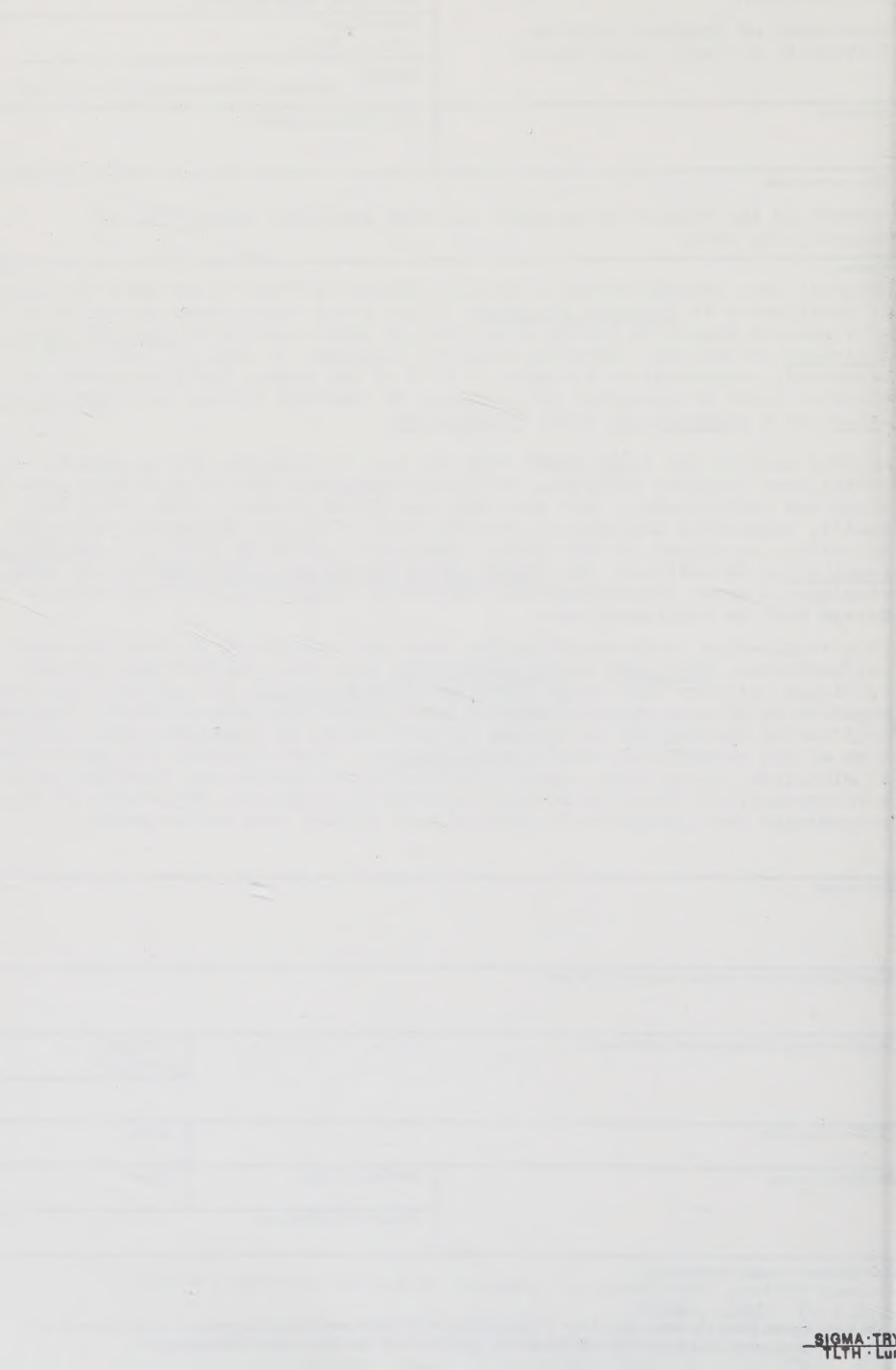
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Subjects were studied during a ten-year period in order to evaluate the risk of development to <u>diabetes mellitus</u>. It was found that normal tolerance to oral glucose signified little or no risk of deterioration to <u>impaired glucose tolerance</u> or manifest diabetes. Impaired tolerance to oral glucose, if left untreated, progressed to diabetes in 29 % of the cases. The development to diabetes could be prevented or postponed by combined therapy with <u>diet regulation</u> and a <u>sulfonylurea</u> drug, <u>tolbutamide</u>. Another part of the study dealt with the use of sulfonylureas in already established diabetes mellitus. In diabetic subjects treated with diet regulation and sulfonylurea, less than half had blood glucose levels below 8.0 mmol/l, indicating therapeutic insufficiency. This may in part be explained by failure to adhere to the dietary regulation and/or by deficient <u>medication compliance</u>. In addition, the <u>steady state plasma concentrations</u> of the drugs displayed a great interindividual difference, suggesting that sulfonylurea dosage must be individualized. In a single-dose study comparing the kinetics and effects of four different sulfonylureas, <u>glipizide</u> and <u>glibenclamide</u> were found to have much greater intrinsic activity than tolbutamide and <u>chlorpropamide</u>. In addition, glipizide appeared to be more rapid-acting and more potent than glibenclamide. However, this latter finding may be related to differences in biopharmaceutic properties of the preparations used. <u>Food intake</u> was found to delay the absorption of glipizide. Accordingly, administration of the drug before breakfast gave a more appropriate reduction of blood glucose in diabetics. Therefore, it is recommended that glipizide is administered half an hour before meals.			
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Signature Gunnar Sartor

Date February 1980



This thesis is based upon the following papers, which are referred to by their Roman numerals:

- I Sartor, G., Scherstén, B., Carlström, S., Melander, A., Nordén, Å. and Persson, G.: Ten-year follow-up of subjects with impaired glucose tolerance: Prevention of diabetes by tolbutamide and diet regulation. *Diabetes* 29, 41-49, 1980.
- II Melander, A., Sartor, G., Wåhlin, E., Scherstén, B. and Bitzén, P -O.: Serum tolbutamide and chlorpropamide concentrations in patients with diabetes mellitus. *British Medical Journal* 1, 142-144, 1978.
- III Sartor, G., Melander, A., Scherstén, B. and Wåhlin-Boll, E.: Influence of food and of age on the single-dose kinetics and effects of tolbutamide and chlorpropamide. *European Journal of Clinical Pharmacology*, in press, 1980.
- IV Sartor, G., Melander, A., Scherstén, B. and Wåhlin-Boll, E.: Serum glibenclamide in diabetic patients, and influence of food on the kinetics and effects of glibenclamide. *Diabetologia* 18, 17-22, 1980.
- V Sartor, G., Melander, A., Scherstén, B. and Wåhlin-Boll, E.: Comparative single-dose kinetics and effects of four sulfonylureas in healthy volunteers. Submitted for publication to *Acta Medica Scandinavica*.
- VI Wåhlin-Boll, E., Melander, A., Sartor, G. and Scherstén, B.: Influence of food intake on the absorption and effect of glipizide in diabetics and in healthy subjects. Submitted for publication to *European Journal of Clinical Pharmacology*.

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INTRODUCTION

The treatment of diabetes mellitus is usually motivated not only by the acute metabolic derangement but also by the great risk for vascular and neuronal damage if the disease is left uncontrolled. This is based on the widespread albeit unproven assumption that strict control not only is beneficial in the short-term perspective but also minimizes the long-term complications. The latter further justify an active search for undetected cases; in particular, it seems urgent to find such subjects as early as possible, i.e. before the disease becomes clinically manifest.

In a diabetes detection campaign started in 1962 in Malmöhus county, numerous subjects were found to have impaired tolerance to oral glucose as defined in a separate study (1). These individuals were assumed to be in an early phase of not insulin-dependent diabetes mellitus (type II). Therefore, it was decided to assess the frequency of diabetes development in such subjects and to examine whether therapy with diet regulation and sulfonylurea administration could prevent or postpone such development. This is the topic of the first part of the present thesis (paper I).

The second part (papers II-VI) deals with the use of sulfonylureas in the treatment of subjects with already established diabetes mellitus. Particular emphasis is laid on the following questions: 1) Is the current use of sulfonylureas optimal or can it be improved? 2) Are there relevant differences between different sulfonylureas? 3) How should sulfonylureas be taken in relation to meals? These aspects have been investigated by a combination of pharmacokinetic and pharmacodynamic studies, carried out both in healthy volunteers and in patients with type II diabetes mellitus.

SUBJECTS

Paper I

A diabetes detection campaign, based on postprandial urine testing with Clinistix^(R), was performed from 1962 to 1965 in Malmöhus county in Sweden. The survey covered 82 % (n = 228,833) of the adult popul-

ation. Glucosuria was found in 1.08 % ($n = 2,477$), and in 2,180 of these a 3 h oral glucose tolerance test (OGTT) was carried out. The diagnostic criteria for evaluation of the OGTT were established from a randomized subset of the adult population born January 20 or July 20 ($n = 5,000$). Of these, 80 % ($n = 4,000$) participated and had no glucosuria when tested postprandially. Through a randomization procedure, 10 % ($n = 400$) were selected, and an OGTT was performed in 311. Of these, 263 had a negative family history of diabetes, and the results obtained in these subjects were set as the normal reference. All 10 blood glucose values above the mean plus 3 standard deviations (SD) were taken to indicate manifest diabetes, and all 10 blood glucose values below the mean plus 2 SD were considered to represent the normal state. Impaired glucose tolerance was defined as the condition when neither the criteria for diabetes nor those for normality were fulfilled.

Of the 2,180 subjects with glucosuria, 578 had impaired glucose tolerance. They were randomized in groups given either no therapy or diet regulation alone or in combination with placebo or tolbutamide. The randomization procedure and the information given to the subjects are described in paper I.

From the subset of the population considered to have a normal OGTT in 1962, 52 men were randomly selected at the time of follow-up (1974-1976). Considerations regarding reclassification, time to follow-up, diagnosis of diabetes, causes of death and drop-outs are given in paper I.

Papers II-VI

Diabetic patients: All diabetic patients studied had been treated with conventional diet regulation. In addition, most patients were on sulfonylurea medication (papers II and IV). The investigations were carried out when the patients attended their regular visit to the out-patient clinics. All patients studied were regular attenders to the clinics and were in a good metabolic balance when selected for the studies. Details are given in the separate papers.

Healthy volunteers: Young male medical students (papers III-VI) volunteered for the studies concerning single-dose kinetics and effects of sulfonylureas. They were all healthy according to a clinical examination and routine blood tests. Elderly volunteers (paper III) were recruited from a group of pensioners who yearly undergo a comprehensive clinical and laboratory examination at the Community Care Center in Dalby. Details are given in the separate papers.

METHODS

Blood glucose

Capillary blood (finger tip) was used in study I and venous blood (cubital vein) in the other studies. The glucose oxidase method (2) with a modification (3) was used in study I and in the diabetic subjects in paper VI, whereas in the other studies the hexokinase method (4) was employed.

Plasma insulin

Plasma insulin was determined by a commercial solid phase radioimmunoassay (Phadebas Insulin Test^(R), Pharmacia, Uppsala, Sweden) (5). The interassay variation (SD) was 5.5 % at 5 m IU/l, 5.8 % at 40 m IU/l and 4.9 % at 160 m IU/l.

Serum sulfonylurea

The serum concentrations of tolbutamide and chlorpropamide were determined by gas chromatography (6; see also papers I-III and V), that of glibenclamide by radioimmunoassay (7; see also papers IV and V), and that of glipizide by high-pressure liquid chromatography (8; see also papers V and VI). The interassay variation (SD) was 5.8 % for tolbutamide, 4.3 % for chlorpropamide, 9.9 % for glibenclamide, and 6.2 % for glipizide.

Oral glucose tolerance test

Oral glucose tolerance tests (OGTT) were carried out in study I. Glucose (30 g/m^2 body surface area) was administered in a 10 % solution between 8 a.m. and 9 a.m. after fasting overnight.

Standardized meal

A standardized breakfast meal was given in studies III-VI. It consisted of 400 ml of low-fat milk, 2 slices (20 g) of white bread with 35 g cheese and 5 g butter, and 150 ml of black coffee without sugar. This yielded a total of about 1800 kJ (430 kcal).

Statistics

The statistical significance of differences was calculated by paired or non-paired Student t-tests, by chi square tests or Wilcoxon's signed-rank test. Correlation tests were carried out by regression analyses. Standard deviation is indicated by SD and standard error of the mean by SEM.

RESULTS AND DISCUSSION

Prevention of diabetes development by diet regulation and tolbutamide

Paper I describes the development of diabetes mellitus in subjects with impaired glucose tolerance (IGT) as compared to that in normal subjects. In addition, this paper deals with the influence of diet regulation and tolbutamide on diabetes development.

At the ten-year follow-up, none of the normal subjects had developed IGT or manifest diabetes, whereas almost one third (29 %) of the IGT subjects progressed to diabetes when left untreated. In contrast, no IGT subject developed diabetes when treated with a combination of diet regulation and tolbutamide 0.5 g t.i.d. Of those with diet regulation, 13 % were diabetic at follow-up. These findings indicate that, while normal glucose tolerance, tested as described, carries little risk of development to impaired glucose tolerance or manifest diabetes, IGT signifies a great risk of progression to diabetes. In addition, the findings suggest that diet regulation in combination with tolbutamide can prevent or postpone such progression.

A previous analysis of this series of subjects (9) had suggested that IGT subjects have a higher than normal cardiovascular morbidity. However, this risk was reduced by the combination of diet regulation and tolbutamide. This accords with the present finding of a diminished dia-

stolic blood pressure and a reduced mean level of serum lipids in the group on diet regulation and tolbutamide. Together, the present and the cited (9) observations support the view that sulfonylureas are beneficial rather than harmful in the long-term perspective.

Other studies (10-13) have failed to show a beneficial effect of sulfonylurea on diabetes morbidity. There are several possible explanations for these discrepancies, such as different ways of recruiting subjects, and differences in the diagnostic criteria for IGT, kind and dosage of the sulfonylurea, medication compliance, time to follow-up, and withdrawal of medication before the re-examination.

As far as drug and dosage are concerned, the dosage of tolbutamide in the present study was 50.% higher than that in the Bedford-study (10) and that in the study by Feldman et al. (11). The study by Stowers (12) used chlorpropamide at an initial dosage (100 mg) that is lower than conventional.

In the present study, the degree of compliance was investigated in contrast to the above-mentioned (10-13). About 50 % of those on medication (irrespective of whether they were kept on tolbutamide or placebo) in the present study admitted that they had ceased their tablet intake before follow-up. Hence some of those allegedly remaining on the drug may not have been taken it appropriately. Indeed, among those claiming that they were still taking the drug, only 82 % had measurable concentrations of tolbutamide in serum.

Another important aspect is that, in the studies referred to, sulfonylurea medication was withdrawn for at least 3 days before the re-examination, whereas in the present study medication was continued until the day before re-examination.

Another difference is the time until follow-up, which was 10 years in the present study, while varying from 3.6 to 7 years in the other studies. It is of interest in this context that, in the present study, there was no observable treatment-associated change in diabetes morbidity until after 7 years (see figure 2, paper I).

The current findings are at utmost variance with those of the University Group Diabetes Program (UGDP) (14) both as to therapeutic efficacy and adverse reactions of tolbutamide. Apart from the fact that the UGDP study dealt with cases of already established diabetes, there are several possible explanations for the apparent differences. Most importantly, recent evaluations of the UGDP material have cast doubt on the conclusions, and particular attention has been focused on the heterogeneity between treatment groups. Thus, there were 70 % females in the placebo group and the mortality ratio for males versus females was 5.3:1, which has probably yielded the false impression of an increased cardiovascular mortality in the tolbutamide-treated group (15). The apparent lack of therapeutic efficacy may be due to a low compliance, as 42 % not attending control visits or admitting no tablet intake were included in the statistical evaluation (16). In addition, the use of a fixed tolbutamide dosage is not in accordance with conventional clinical routines in the treatment of established diabetes.

Individualization of sulfonylurea dosage

In order to assess whether the conventional use of sulfonylureas is optimal, the steady state concentrations of tolbutamide, chlorpropamide, and glibenclamide and the fasting blood glucose levels were measured in 134 patients with type II diabetes, treated with diet regulation in combination with one of these drugs since at least one year (papers II and IV). It was found that only few patients had completely normal fasting blood glucose levels (5.5 mmol/l) and that less than half had concentrations below 8.0 mmol/l. This indicates that the therapy was insufficient. Because the intention was to study the therapeutic effect of conventional routines, intervention with dietary and medication habits was deliberately avoided. Accordingly, failure to adhere to dietary regulation probably explains part of the therapeutic insufficiency. Moreover, deficient compliance with medication is another likely explanation; indeed, several patients were found to have very low or unmeasurable steady state concentrations of the drugs.

An additional explanation of the therapeutic failures emerged from the observation that, although the dosage variation was only four-fold for chlorpropamide, six-fold for tolbutamide and ten-fold for glibenclamide, the interindividual differences in the steady state concentrations of the drugs were very great, ranging from close to zero to 882 $\mu\text{mol/l}$ for chlorpropamide, from close to zero to 370 $\mu\text{mol/l}$ for tolbutamide, and from close to zero to 1520 nmol/l for glibenclamide. In fact, there was no correlation between the dosage prescribed and the steady state concentration of the drug(s).

No simple relation between drug concentrations and fasting blood glucose levels could be observed, and should not be expected as food intake was deliberately not standardized. Nevertheless, the findings suggest that the dosage of sulfonylureas should be more individualized than is currently done. According to unpublished observations, this seems to be true also for another sulfonylurea, glipizide.

Differences between sulfonylureas

Sulfonylureas are used in the treatment of diabetes mellitus in order to normalize glucose economy. In particular, it seems important to enhance the disposition of the large carbohydrate load following meals. Thus, the sulfonylurea should be potent and rapid-acting. Preferably, they should also be short-acting, to avoid hypoglycaemia between meals. In an attempt to compare these qualities, i.e. potency, rapidity and duration, single standard doses of tolbutamide (0.5 g), chlorpropamide (0.25 g), glibenclamide (5 mg) and glipizide (5 mg) were given both with and without a standardized breakfast meal to healthy volunteers (paper V). Despite the limited possibility to draw clinically relevant conclusions from single-dose studies, the results support the notion that glibenclamide and glipizide are at least 1,000 times as potent as tolbutamide and chlorpropamide, and that this may result from a true difference in intrinsic activity. Glipizide seemed to promote both a more pronounced and a more rapid increase of plasma insulin and a correspondingly greater and faster blood glucose reduction than did glibenclamide. This might be due to inherent differences in the intrinsic activity of glipizide and glibenclamide. However, it is quite possible that the findings are due solely to biopharmaceutic

differences, yielding a greater bioavailability and more rapid absorption of glipizide from Min(i)diab^(R) tablets than of glibenclamide from Daonil^(R) tablets.

The half-lives of glibenclamide (1.8 h) and glipizide (4.3 h) were much shorter than those of tolbutamide (7.2 h) and chlorpropamide (34 h). The very short half-life of glibenclamide is surprising in the light of the clinical experience that glibenclamide may provoke long-lasting hypoglycaemia (17-18). However, it is possible that the methods employed (7-8) are not sensitive enough to allow accurate determinations of the true elimination phases of glibenclamide and glipizide; indeed, when ¹⁴C-labelled drugs were used, there was evidence of slow elimination from a deep compartment (19).

In addition, it cannot be excluded that the active metabolite of glibenclamide accumulates in patients with impaired renal function, thus prolonging the hypoglycaemic effect of glibenclamide (20).

Optimal relation between intake of meals and administration of sulfonylureas

As appropriate diet regulation is a major factor in the control of diabetes, the relation between food intake and administration of sulfonylureas is of particular importance. Therefore, studies were performed as to the influence of food on the single-dose kinetics and effects of tolbutamide, chlorpropamide (paper III), glibenclamide (paper IV) and glipizide (paper VI) in healthy volunteers.

Food intake evoked a statistically significant but clinically irrelevant reduction of the peak concentration of chlorpropamide, but affected neither the rate of absorption, bioavailability nor the elimination rate of tolbutamide, chlorpropamide or glibenclamide. The kinetic profiles of tolbutamide and chlorpropamide were essentially similar in young (22 - 28 years of age) and in elderly (74 - 75 years of age) volunteers (paper III). This lends credence to the assumption that the observations made in young subjects probably are relevant also for type II diabetics, who usually are over the age of 55.

An additional observation was that each drug was capable to reduce blood glucose levels without promoting an increase in peripheral insulin concentrations. This is in accordance with the evidence that sulfonylureas may have extrapancreatic actions (21). Sulfonylureas apparently reduce glucose output from the liver, and this may be due to inhibition of hepatic insulinase (22), inhibition of glucagon-induced hepatic gluconeogenesis (23) and/or other interference with glucose disposition by the liver. In support of this, it was seen (paper III) that tolbutamide elicited a significant glucose reduction at a time when the drug concentration in systemic blood still was close to zero. It is possible that the concurrent porto-hepatic drug concentration was much higher and capable of evoking an inhibition of glucose release from the liver. Another possible extrapancreatic effect of sulfonylureas is that they enhance the number and/or activity of insulin receptors (24-25).

In contrast to the other three drugs, glipizide displayed a delayed absorption - about 30 minutes - when taken together with food (paper VI). This food-induced delay suggests that glipizide should be administered before, rather than together with the meal. To evaluate whether such a regimen would be of clinical value, 14 diabetics without previous sulfonylurea medication were examined after intake of glipizide both together with, and 30 min before, a standardized breakfast meal (paper VI). At breakfast start, and for 45 min thereafter, glipizide plasma concentrations were pronouncedly higher when the drug was given 30 min before, than when given concurrently with, the meal. As a consequence, the increase of plasma insulin occurred earlier. This was accompanied by a lower postprandial blood glucose peak and a greater subsequent reduction in blood glucose.

Thus, concurrent intake of food seems to delay the absorption of glipizide. Administration of the drug half an hour before breakfast yields a more appropriate relation between the blood concentrations of glipizide and the metabolic impact of the meal than does concurrent administration of drug and meal.

GENERAL CONCLUSIONS

The present thesis is an attempt to assess the frequency of diabetes development in subjects with impaired tolerance to oral glucose (IGT), and to examine whether a combination of diet regulation and tolbutamide could prevent or postpone such development. In addition, the thesis deals with the use of sulfonylureas in the treatment of subjects with already established diabetes mellitus.

The findings can be summarized as follows.

1. Normal glucose tolerance carries little risk of development to IGT or manifest diabetes, whereas IGT signifies a great risk of progression to manifest diabetes. In addition, the findings suggest that diet regulation in combination with sulfonylurea can prevent or postpone such progression.
2. In subjects with already manifest diabetes conventionally treated with diet regulation in combination with tolbutamide, chlorpropamide or glibenclamide, only few had completely normal fasting blood glucose levels (5.5 mmol/l) and less than half had concentrations below 8.0 mmol/l. Thus, the therapy was insufficient. Failure to adhere to dietary regulation or to comply with medication may explain part of this insufficiency. However, an additional explanation is that the dosage has to be more individualized, as suggested by a very great interindividual difference in the steady state concentrations of each drug.
3. As judged from single-dose studies with sulfonylurea in healthy volunteers, glipizide and glibenclamide appeared much more potent than tolbutamide and chlorpropamide, and this seemed to result from a true difference in intrinsic activity. Glipizide evoked a more pronounced and more rapid increase of plasma insulin and a correspondingly greater and faster blood glucose reduction than did glibenclamide. However, it is quite possible that this is due to biopharmaceutic differences rather than to inherent differences in intrinsic activity.
4. Concurrent intake of food may delay the absorption of glipizide. As compared to concurrent intake of drug and meal, administration of the drug half an hour before breakfast was found to yield a

more appropriate relation between the blood concentrations of glipizide and the metabolic impact of the meal, reflected as an earlier release of insulin and a more pronounced reduction of blood glucose. Hence, it is recommended that glipizide is given half an hour before meals.

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REFERENCES

1. Lundquist, I., Nordén, Å. and Scherstén, B.: Studies in subjects with positive postprandial Clinistix^(R) test. Acta Medica Scandinavica 187, 163-168, 1970.
2. Marks, V.: An improved glucose-oxidase method for determining blood, c.s.f. and urine glucose levels. Clinica Chimica Acta 4, 395-400, 1959.

3. Scherstén, B.: Clinical evaluation of a rapid enzyme strip method (Dextrostix) for blood glucose estimation. *Acta Medica Scandinavica* 178, 583-590, 1965.
4. Coburn, H.J. and Carrol, J.J.: Improved manual and automated colorimetric determination of serum glucose, with use of hexokinase and glucose-6-phosphate dehydrogenase. *Clinical Chemistry* 19, 127-130, 1973.
5. Wide, L., Axén, R. and Porath, J.: Radioimmunosorbent assay for proteins. Chemical couplings of antibodies to insoluble Dextran. *Immunochemistry* 4, 381-386, 1967.
6. Prescott, L.F. and Redman, D.R.: Gas-liquid chromatographic estimation of tolbutamide and chlorpropamide in plasma. *Journal of Pharmacy and Pharmacology* 24, 713-716, 1972.
7. Hrtska, V.E. and Schmidt, F.M.: Radioimmunologische Bestimmung von Glibenclamid (Abstract). 8. Kongress der deutschen Diabetes-Gesellschaft, München 1973.
8. Wählin-Boll, E. and Melander, A.: High-pressure liquid chromatographic determination of glipizide and some other sulfonylurea drugs in serum. *Journal of Chromatography* 164, 541-546, 1979.
9. Persson, G.: Cardiovascular complications in diabetics and subjects with reduced glucose tolerance. *Acta Medica Scandinavica, Supplement* 605, 1977.
10. Keen, H., Jarret, R.J. and Fuller, J.H.: Tolbutamide and arterial disease in borderline diabetics. In: *Proceedings, VIII Congress of the International Diabetes Federation*. Malaisse, W.J., and Pirart, J., Eds. Amsterdam, Excerpta Medica, 1973, pp. 588-602.
11. Feldman, R., Crawford, D., Elashoff, R. and Glass, A.: Progress report on the prophylactic use of oral hypoglycemic drugs in asymptomatic diabetes: neurovascular studies. *Advances in Metabolic Disorders* 2, Supplement 2, 557-567, 1973.
12. Stowers, J.M.: Treatment of chemical diabetes with chlorpropamide and the associated mortality. *Advances in Metabolic Disorders* 2, Supplement 2, 549-555, 1973.
13. Logie, A.W., Stowers, J.M. and Dingwall-Fordyce, I.: Longitudinal study of untreated chemical diabetes. *British Medical Journal* 4, 630-632, 1974.

14. University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. *Diabetes* 19, Supplement 2, 1970.
15. Williamson, J.R. and Kilo, C.: The present outlook for oral hypoglycemic agents. In: Satellite Symposium to the 10th Congress of the International Diabetes Federation. Budapest, 1979.
16. Williamson, J.R. and Kilo, C.: Effect of tolbutamide treatment on cardiovascular mortality in the University Group Diabetes Program. International Congress Series No. 481. *Excerpta Medica*, 1979.
17. Clarke, B.F. and Campbell, I.W.: Long-term comparative trial of glibenclamide and chlorpropamide in diet-failed, maturity-onset diabetics. *The Lancet* i, 246-248, 1975.
18. DeVigan, C., Delporte, M.P., Thomas, M. and Perrault, M.: Les accidents hypoglycémiques de thérapeutiques orales du diabète. *La Nouvelle Presse Médicale* 5, 906-910, 1976.
19. Balant, L., Fabre, J. and Zahnd, G.R.: Comparison of the pharmacokinetics of glipizide and glibenclamide in man. *European Journal of Clinical Pharmacology* 8, 63-69, 1975.
20. Schmidt, F.H.: Plasma levels and excretion of glibenclamide in renal insufficiency. *Atti delle giornate di diabetologia del Mediterraneo*, pp. 1-18. Milano: Boehringer Biochemica s.r.l., 1975.
21. Feldman, J.M. and Lebovitz, H.E.: Appraisal of the extrapancreatic actions of sulfonylureas. *Archives of Internal Medicine* 123, 314-322, 1969.
22. Marshall, A., Gingerich, R.L. and Wright, P.H.: Hepatic effect of sulfonylureas. *Metabolism* 19, 1046-1052, 1970.
23. Blumenthal, S.A. and Whitmer, K.R.: Hepatic effect of chlorpropamide. Inhibition of glucagon-stimulated gluconeogenesis in perfused livers of fasted rats. *Diabetes* 28, 646-650, 1979.
24. Olefsky, J.M. and Reaven, G.M.: Effects of sulfonylurea therapy on insulin binding to mononuclear leucocytes of diabetic patients. *American Journal of Medicine* 60, 89-95, 1976.
25. Beck-Nielsen, H., Pedersen, O. and Lindskov, H.O.: Increased insulin sensitivity and cellular insulin binding in obese diabetics following treatment with glibenclamide. *Acta Endocrinologica* 90, 451-462, 1979.

COMPARATIVE SINGLE-DOSE KINETICS AND EFFECTS OF FOUR SULFONYLUREAS IN
HEALTHY VOLUNTEERS

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and Dalby, Sweden.

SUMMARY

The single-dose kinetics and effects of tolbutamide (500 mg), chlorpropamide (250 mg), glibenclamide (5 mg) and glipizide (5 mg) were compared in 7 healthy male volunteers, by measurements of the serum concentrations of the drugs and of plasma insulin and blood glucose. The drugs were given both on an empty stomach and together with a standardized breakfast. The concentrations of tolbutamide and chlorpropamide were measured by gas chromatography, those of glipizide with high-pressure liquid chromatography, those of glibenclamide and insulin by radioimmunoassay and those of glucose by the hexokinase method.

Glipizide and glibenclamide were more potent inducers of insulin release and blood glucose reduction than were tolbutamide and chlorpropamide. As the concentrations of the two former were in the range of nmol/l while those of tolbutamide and chlorpropamide were in the μ mol/l range, the findings support the notion that the intrinsic activity of the two second-generation sulfonylureas is at least 1 000 times greater than that of the two first-generation drugs. Glipizide seemed to be a more potent and more rapid insulin releaser than glibenclamide, but this may be secondary to biopharmaceutic differences between the two preparations used; the bioavailability of glipizide was apparently greater than that of glibenclamide. Both glibenclamide ($t_{1/2} = 1.8$ h) and glipizide ($t_{1/2} = 4.3$ h) showed much shorter elimination half-lives than did tolbutamide (7 h) and chlorpropamide (34 h). It seems probable, however, that these half-lives are not fully informative as to the duration of action of the drugs.

A recent 10-year follow-up indicates that impaired glucose tolerance, if left untreated, carries a great risk of development into manifest diabetes, but that this development can be prevented or postponed by a combination of diet regulation and tolbutamide (13). In addition, another analysis of the same material has shown that this medication reduces rather than enhances cardiovascular morbidity (9). These findings suggest that sulfonylurea drugs are beneficial rather than harmful, and this has reawakened interest in the search of an optimal sulfonylurea preparation.

The aim of sulfonylurea treatment is normalization of glucose economy. In particular, it is important to enhance the disposition of the large carbohydrate loads that follow each meal. On the other hand, the sulfonylurea effect should not prevail between meals, and the drug should not be liable to provoke long-lasting hypoglycemia. Accordingly, the sulfonylurea should be as potent, rapid-acting and short-acting as possible. In an attempt to compare these capacities of tolbutamide, chlorpropamide, glibenclamide and glipizide, single standard doses of these drugs were given both with and without a standardized breakfast to seven healthy volunteers. The effects on plasma insulin and blood glucose were recorded together with the concentration profiles of each drug.

MATERIAL AND METHODS

Subjects

Seven male volunteers participated in the study. They were considered healthy as judged by conventional physical examinations and routine blood tests. Their mean ages and per cent ideal body weights were 26.2 ($\pm$ SD 1.9) years (range 23.5 - 29) and 96.8 ($\pm$ SD 5.0) per cent (range 90.1 - 101.4). Each subject was extensively informed and gave written consent.

Protocol

On 9 different mornings, with intervals of at least one week, the subjects came to the laboratory after 10 h fasting (10 p.m. - 8 a.m.). Each subject underwent each of the following treatments, 1: a stand-

ardized breakfast meal without drug intake, 2 - 5: meal plus 500 mg tolbutamide*, 250 mg chlorpropamide**, 5 mg glibenclamide*** or 5 mg glipizide****, and 6 - 9: the same drugs without the meal (fasting continued for another 4 h). The standardized meal consisted of 400 ml low-fat milk, 20 g white bread with 5 g butter and 35 g cheese, and 150 ml non-sweetened black coffee, yielding a total energy of 430 kcal or 1 800 kJ.

Analyses

Serial blood samples were obtained through an indwelling antebrachial venous polyethylene catheter. Blood glucose and plasma insulin were followed for 3 h. Blood glucose concentrations were determined by the hexokinase method (4) and plasma insulin concentrations were measured by a commercial solid phase radioimmunoassay (Phadebas Insulin-Test^(R), Pharmacia, Uppsala, Sweden). The serum concentrations of the drugs were monitored for 24-48 h. Tolbutamide and chlorpropamide were determined by gas chromatography (11). The possibility of chromatographic pyrolysis of sulfonylurea was avoided by using an all-glass system and a low injection temperature. The inter-assay variability was 5.1 % (SD of a serum pool value). Glipizide was measured by a high-pressure liquid chromatographic assay, having a sensitivity of 20 nmol/l and an inter-assay variability of 6.2 % (15). Glibenclamide was determined by radioimmunoassay (7). The antibody reacts not only with glibenclamide but also with its hydroxylated active metabolite. However, as the metabolite normally is present only in minute amounts and has a very short half-life (14), its interference would be negligible in a single-dose study on healthy volunteers. The assay sensitivity was 20 nmol/l, and the inter-assay variation was 9.9 %.

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- * Artosin^(R), Boehringer Mannheim GmbH, Mannheim, Federal Republic of Germany.
- ** Diabines(e)^(R), Pfizer Corp., Groton, Conn., U.S.A.
- *** Daonil^(R), Hoechst, AG. Frankfurt, Federal Republic of Germany.
- **** Min(i)diab^(R), Carlo Erba, Milano, Italy.

Calculations

The serum concentrations of the different drugs were plotted against time. Peak concentration was defined as the highest value recorded. As the absorption and elimination phases could not be safely distinguished from each other, no calculations were carried out as to absorption kinetics, but the elimination half-life ($t_{\frac{1}{2}}$) was calculated by regression analysis. The area under the curve (AUC) was estimated by the trapezoidal rule. The statistical significance of differences was calculated by Student's paired t-tests on intra-individual data pairs and by Wilcoxon's signed-rank test.

RESULTS

Drug concentrations in serum

Fig. 1 shows the single-dose kinetics of tolbutamide (500 mg), chlorpropamide (250 mg) (Fig. 1 a) glibenclamide (5 mg) and glipizide (5 mg) (Fig. 1 b) ingested in the fasting state. The kinetic data both during fasting and non-fasting conditions are given in Table I. It can be seen that the two former drugs yielded serum concentrations of several $\mu\text{mol/l}$ while those of the two latter were in the nmol/l range. The elimination of chlorpropamide (mean of 34 h in the fasting state) was much slower than that of tolbutamide (7.2 h; $p < 0.001$), which in turn was slower ($p < 0.01$) than that of glipizide (4.3 h) and that of glibenclamide, which was shortest of all (1.8 h; $p < 0.05$ vs. glipizide). Similar $t_{\frac{1}{2}}$ figures were recorded when the drugs were taken in the non-fasting state (Table I).

Both in the fasting and the non-fasting state, the mean peak concentration of glipizide was numerically but not significantly greater than that of glibenclamide. A significant difference was recorded with respect to the time to reach peak concentration; in the fasting state, the mean t_{max} was 2 h for glipizide while that of glibenclamide was 3.5 h ($p < 0.05$). The mean AUC of glibenclamide was smaller than that of glipizide both in the fasting and in the non-fasting state; the latter but not the former difference reached statistical significance ($p < 0.05$).

Plasma insulin

Fig. 2 demonstrates the plasma insulin profiles following intake of the four drugs in the fasting state. The pre-exposure mean values did not differ significantly. Glipizide promoted an increase in plasma insulin that was significantly ($p < 0.05$) above control at 45, 60, and 75 min after drug intake. The increments seen following administration of glibenclamide and tolbutamide did not reach statistical significance. Chlorpropamide evoked hardly any change at all.

Table II shows the plasma insulin levels following intake of the four drugs both with and without the standardized breakfast. The pre-exposure values were not significantly different. Both glipizide and glibenclamide yielded greater plasma insulin increments than did the meal only. However, statistical significance was reached only for glibenclamide, at 90, 120 and 150 min ($p < 0.05$). No significant difference was recorded at any interval between the plasma insulin concentrations following glipizide plus meal and glibenclamide plus meal.

Blood glucose

The blood glucose profiles following intake of the four drugs in the fasting state are shown in Fig. 3. Significant reductions ($p < 0.05$) of the blood glucose concentrations were recorded at 45 and 60 min (tolbutamide and glipizide), at 75, 90, 120 and 150 min (tolbutamide, glipizide and glibenclamide) and at 180 min (glipizide and glibenclamide). The mean numerical blood glucose reduction seen following chlorpropamide did not reach statistical significance at any interval studied. Glipizide seemed to evoke a stronger and more rapid glucose diminution than glibenclamide, but the difference did not reach statistical significance at any interval studied. Both these drugs, on the other hand, evoked glucose reductions that were significantly ($p < 0.05$) greater than those following tolbutamide at 60, 75, 90 (glipizide), 120 and 180 (glipizide and glibenclamide) min.

Concurrent administration of drugs and meal (Table III) yielded lower blood glucose increments than did the meal only; significance ($p < 0.05$) was reached both with glipizide (at 75 - 180 min), and glibenclamide (at 150 min).

DISCUSSION

The kinetic characteristics of sulfonylureas have been described previously (2, 17), and the observations made in the present study are essentially in agreement therewith. However, there seem to be few studies concerning the comparative aspects, and this was the major concern of the concurrent investigation. Particular emphasis was laid on differences in intrinsic activity and in rapidity of effect.

The drug measurements showed that the plasma concentrations of glipizide and glibenclamide were in the range of nmol/l while those of tolbutamide and chlorpropamide were in the μ mol/l range. As both glipizide and glibenclamide were at least as effective as the two other drugs (*vide infra*), the findings support the notion that the intrinsic activity of the two second-generation sulfonylureas is at least 1 000 times greater than that of the two first-generation drugs.

As far as the difference between glipizide and glibenclamide is concerned, it was seen that, in the fasting state, glipizide induced a more pronounced increase of plasma insulin than did glibenclamide. Moreover, glipizide seemed to promote the greatest blood glucose reduction. Furthermore, hypoglycemic reactions were reported by five subjects after glipizide but by only two after glibenclamide.

These findings could signify that glipizide is a more potent insulin releaser than glibenclamide. However, the seemingly stronger effect of glipizide may be secondary to biopharmaceutic differences between Min(i)diab^(R) and Daonil^(R) tablets; at the same dosage, at least 40 % more glipizide than glibenclamide reached systemic circulation even though the molecular weights differ by only 10 % (446 and 494, respectively). Thus, it seems probable that the bioavailability of glipizide from Min(i)diab^(R) tablets is greater than that of glibenclamide from currently available Daonil^(R) tablets. Accordingly, the question whether glipizide and glibenclamide differ in intrinsic activity remains unanswered by the present study. Another complication in the comparison between the two drugs is that concomitant food intake reduces the absorption rate and hence the effect of glipizide (16), while no such influence has been recorded for glibenclamide (12). A similar tendency was seen in the present study, although the diff-

erence did not reach statistical significance.

Another finding that may relate to biopharmaceutic differences concerns the rapidity of effect. Glipizide seemed to be more rapidly absorbed than glibenclamide, and the time to reach peak concentration was significantly longer for glibenclamide (3.5 h) than for glipizide (2 h), even though the peak concentration was greater for the latter than for the former. Thus, it is likely that glipizide reached its minimum effective concentration more rapidly than did glibenclamide. This may explain both the impression that glipizide yielded a more rapid effect and the apparently higher potency of this drug (vide supra). Similarly, the slight (tolbutamide) or virtually absent (chlorpropamide) effect of the two first-generation sulfonylureas may be due not only to their weaker intrinsic activity but also to slower absorption, as compared to the second-generation drugs.

The present findings confirm that, of the four drugs studied, chlorpropamide by far has the longest elimination half-life, exceeding 24 h in each subject, with a (fasting) mean of 34 h (cf. 17). In addition, the estimated half-life of tolbutamide, about 7 h (cf. 17), was much longer than those of glipizide and glibenclamide. Furthermore, the latter displayed the shortest elimination half-life of the four drugs, with a mean of only 1.8 h (fasting) as compared to 4.3 h for glipizide. Assuming that the duration of action of each sulfonylurea is related to its plasma elimination half-life, chlorpropamide would be the most long-acting one, and glibenclamide the one with the shortest duration of action. The latter assumption gets support from recent studies suggesting that, while the therapeutic effect of glipizide can be maintained when this drug is given once daily (1, 6, 8), the effect of glibenclamide is reduced when this drug is given once daily as compared to administration twice daily (6). On the other hand, the concept of glibenclamide as a short-acting sulfonylurea is contradicted by much evidence (10) and by the widespread clinical experience that glibenclamide may provoke long-lasting hypoglycaemia (3, 5).

The apparent contradiction between the very short half-life and the allegedly long effect duration of glibenclamide may have several explanations. Firstly, it is possible that the sensitivity of the curr-

ently employed methods is not sufficient to allow accurate determinations of the true elimination phase of glibenclamide and glipizide. Indeed, studies using ^{14}C -labelled drugs suggest that both drugs penetrate a deep compartment from which they are only slowly eliminated (2). It cannot be excluded, moreover, that although the active metabolite of glibenclamide has a very short half-life in healthy subjects (14), it may accumulate in patients with impaired renal functions and hence prolong its effect.

To summarize: Despite the limited possibility to draw clinically pertinent conclusions from single-dose studies in healthy volunteers, the findings support the concept that glipizide and glibenclamide are much more potent sulfonylureas than tolbutamide and chlorpropamide, and that this is due to a major difference in intrinsic activity. Glipizide appears to be more potent and rapid-acting than glibenclamide, but this may simply be due to differences in the biopharmaceutics of Min(i)diab^(R) and Daonil^(R) tablets. Both glibenclamide and glipizide seem to have short elimination half-lives, but these are probably not informative as to the duration of action of these drugs.

ACKNOWLEDGEMENTS

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REFERENCES

1. Almér, L.-O., Johansson, E., Melander, A. & Wåhlin-Boll, E.: Influence of discontinuous and continuous sulfonylurea exposure on the secretion, disposition and effect of insulin in diabetics. Diabetes (Submitted for publication), 1980.
2. Balant, L., Fabre, J. & Zahnd, G.R.: Comparison of the pharmacokinetics of glipizide and glibenclamide in man. Europ. J. Clin. Pharmacol. 8:63, 1975.
3. Clarke, B.F. & Campbell, I.W.: Long-term comparative trial of glibenclamide and chlorpropamide in diet-failed, maturity-onset diabetics. Lancet 1:246, 1975.

4. Coburn, H.J. & Carroll, J.J.: Improved manual and automated colorimetric determination of serum glucose, with use of hexokinase and glucose-6-phosphate dehydrogenase. *Clin. Chem.* 19:127, 1973.
5. De Vigan, C., Delporte, M.P., Thomas, M. & Perrault, M.: Les accidents hypoglycémiques des thérapeutiques orales du diabète. *Nouv. Presse. Med.* 5:906, 1976.
6. Groop, L. & Harno, K.: The diurnal pattern of blood glucose and plasma insulin during glibenclamide and glipizide treatment in elderly diabetics. *Acta Endocrin.* 91 (Suppl 227), 1979.
7. Hrtska, V.E. & Schmidt, F.M.: Radioimmunologische Bestimmung von Glibenklamid. Abstract 8 Kongress der deutschen Diabetes-Gesellschaft, München, 1973.
8. Östman, J., Jansson, B. & Weiner, L.: Relationship between therapeutic effect and bioavailability of glipizide in maturity-onset diabetes mellitus. *Excerpta Medica. Internat. Congr. Ser. No. 481.* (Abstract), 1979.
9. Persson, G.: Cardiovascular complications in diabetics and subjects with reduced glucose tolerance. *Acta Med. Scand. Suppl* 605, 1977.
10. Pfeiffer, E.F.: Sulfonylureas: Newer aspects of pharmacology and clinical efficacy. *In: Diabetes* (ed. W.J. Malaisse and J. Pirart), *Excerpta Medica*, 1973, p. 563.
11. Prescott, L.F. & Redman, D.R.: Gas liquid chromatographic estimation of tolbutamide and chlorpropamide in plasma. *J. Pharm. Pharmacol.* 24:713, 1972.
12. Sartor, G., Melander, A., Scherstén, B. & Wählin-Boll, E.: Serum glibenclamide in diabetic patients, and influence of food on the kinetics and effects of glibenclamide. *Diabetologia* 18:17, 1980.
13. Sartor, G., Scherstén, B., Carlström, S., Melander, A., Nordén, Å. & Persson, G.: Ten-year follow-up of subjects with impaired glucose tolerance: Prevention of diabetes by tolbutamide and diet regulation. *Diabetes* 29:41, 1980.
14. Schmidt, F.H.: Plasma levels and excretion of glibenclamide in renal insufficiency. *Atti delle giornate di diabetologia del Mediterraneo*, pp. 1-18. Milano: Boehringer Biochem s.r.l. 1975.
15. Wählin-Boll, E. & Melander, A.: High-pressure liquid chromatographic determination of glipizide and some other sulfonylurea drugs in serum. *J. Chromatogr.* 164:541, 1979.

16. Wählin-Boll, E., Melander, A., Sartor, G. & Scherstén, B.: Influence of food intake on the absorption and effect of glipizide in diabetics and in healthy subjects. Eur. J. Clin. Pharmacol. (submitted for publication) 1980.
17. West, K.M. & Johnson, P.C.: The comparative pharmacology of tolbutamide, carbutamide, chlorpropamide and metahexamide in man. Metabolism 3:596, 1959.

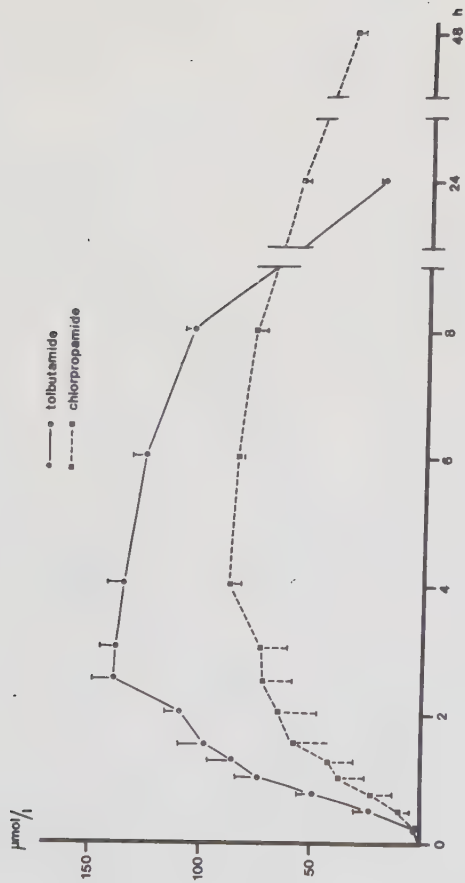


Fig. 1 a: Serum concentrations (mean + SEM) of tolbutamide (500 mg) and chlorpropamide (250 mg) in seven healthy volunteers following intake on an empty stomach. The calculated kinetic data are given in Table I.

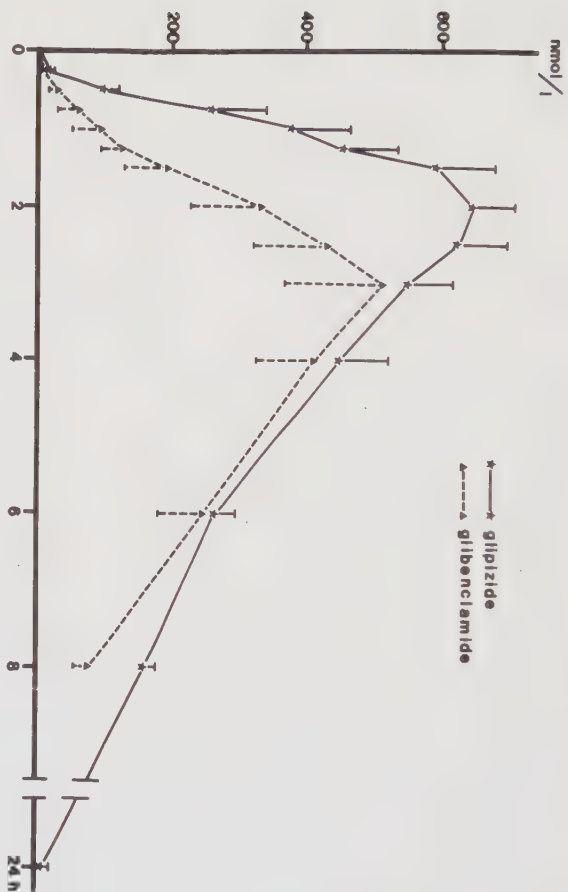


Fig. 1 b: Serum concentrations (mean + SEM) of glipizide (5 mg) and glipizide (5 mg) in seven healthy volunteers following intake on an empty stomach. The calculated kinetic data are given in Table I.

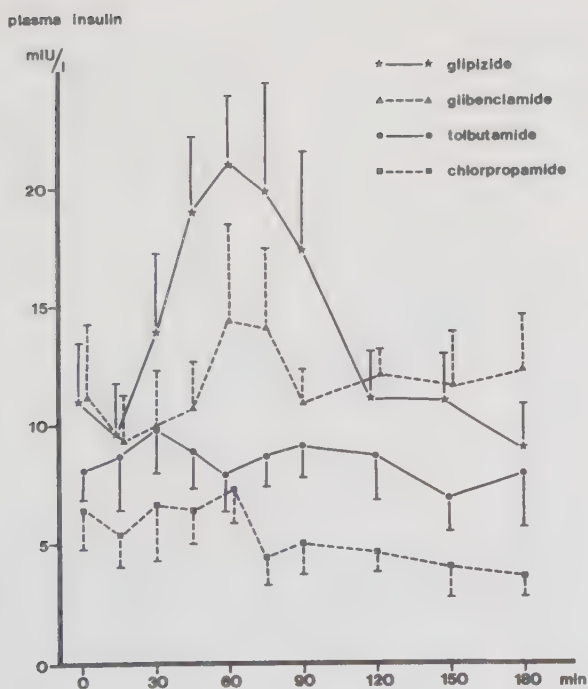


Fig. 2: Plasma insulin concentrations (mean + SEM) in seven healthy volunteers following intake on an empty stomach of tolbutamide (500 mg), chlorpropamide (250 mg), glibenclamide (5 mg) and glipizide (5 mg). The corresponding figures are given in Table II.

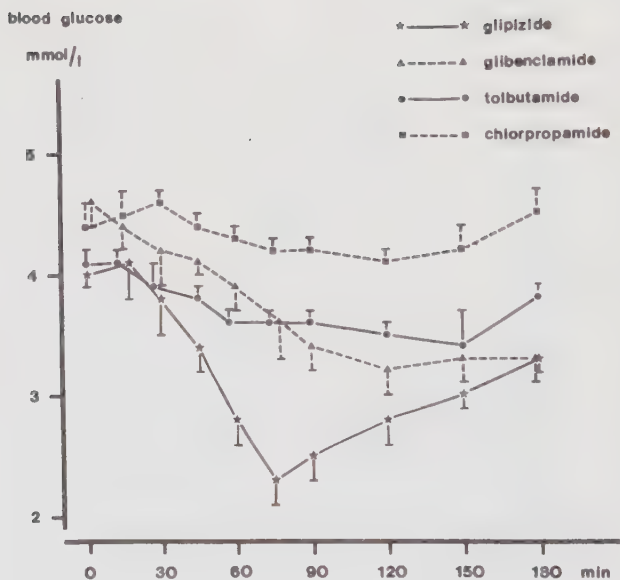


Fig. 3: Blood glucose concentrations (mean + SEM) in seven healthy volunteers following intake on an empty stomach of tolbutamide (500 mg), chlorpropamide (250 mg), glibenclamide (5 mg) and glipizide (5 mg). The corresponding figures are given in Table II.

TABLE I

Pharmacokinetic parameters of four different sulfonylureas in seven healthy volunteers following a single oral dose ingested both on an empty stomach and together with a standardized breakfast. A) tolbutamide 500 mg; B) chlorpropamide 250 mg; C) glibenclamide 5 mg; D) glipizide 5 mg. $C_{\max}$ = peak concentration; $t_{\max}$ = time to peak concentration; $t_{1/2}$ = elimination half-life; AUC = area under the concentration curve. Means ($\pm$ SD) indicated. Statistical significance calculated by paired t -tests on intraindividual data pairs.

	A Tolbutamide	B Chlorpropamide	C Glibenclamide	D Glipizide
	F A S T I N G			
$C_{\max}$ ($\mu\text{mol/l}$)	153 $\pm$ 22	100 $\pm$ 10	0.592 $\pm$ 0.341	0.703 $\pm$ 0.200
range	122 - 178	87 - 112	0.231 - 1.182	0.346 - 0.916
$t_{\max}$ (h)	3.4 $\pm$ 0.7	3.2 $\pm$ 1.5	3.4 $\pm$ 1.2	2.1 $\pm$ 0.5
range	2.5 - 4.1	1.5 - 5.5	2.5 - 6	1.5 - 2.5
$t_{1/2}$ (h)	7.2 $\pm$ 0.7	34 $\pm$ 8	1.8 $\pm$ 0.8	4.3 $\pm$ 1.9
range	6.1 $\pm$ 8.0	21 - 43	1.1 - 2.8	2.5 - 7.3
AUC ($\mu\text{mol} \times \text{h} \times \text{l}^{-1}$)	1976 $\pm$ 200*	2806 $\pm$ 415**	2.109 $\pm$ 1.088***	2.963 $\pm$ 0.794***
range	1587 - 2180	2121 - 3317	0.706 - 3.727	1.764 - 4.385

Table I continues

TABLE I continued

NON - F A S T I N G

$C_{\max}$ ($\mu\text{mol/l}$)	150 ± 23	86 ± 13	0.591 ± 0.130	0.717 ± 0.153
range	122 - 192	65 - 101	$0.453 - 0.868$	$0.496 - 0.884$
$t_{\max}$ (h)	4.0 ± 22	5.4 ± 2.2	2.6 ± 0.8	2.4 ± 0.5
range	1.5 - 7.9	1.3 - 8.2	2 - 4	1.5 - 3.0
$t_{1/2}$ (h)	7.0 ± 0.8	40 ± 11	1.6 ± 0.2	3.9 ± 1.6
range	5.4 - 7.9	26 - 56	1.2 - 1.8	2.0 - 5.7
AUC ($\mu\text{mol} \times \text{h} \times \text{l}^{-1}$)	$1825 \pm 205^*$	$2728 \pm 503^{**}$	$2.261 \pm 0.617^{***}$	$2.957 \pm 0.294^{***}$
range	1571 - 2152	1997 - 3295	$1.920 - 2.299$	$2.560 - 3.343$

* 0-24 h
 ** 0-48 h
 *** 0-8 h

TABLE II

Plasma insulin levels in seven healthy volunteers following a single oral dose ingested both on an empty stomach and together with a standardized breakfast. A) tolbutamide 500 mg; B) chlorpropamide 250 mg; C) glibenclamide 5 mg; D) glipizide 5 mg. Statistical significance is indicated in text. Means ($\pm$ SEM) indicated.

	Time after intake of drug and/or meal (min)									
	0	15	30	45	60	75	90	120	150	180
A	8 $\pm$ 1	9 $\pm$ 2	10 $\pm$ 2	9 $\pm$ 2	8 $\pm$ 2	9 $\pm$ 2	9 $\pm$ 1	9 $\pm$ 2	7 $\pm$ 2	8 $\pm$ 2
B	6 $\pm$ 2	5 $\pm$ 2	7 $\pm$ 2	6 $\pm$ 2	7 $\pm$ 2	4 $\pm$ 1	5 $\pm$ 1	5 $\pm$ 1	4 $\pm$ 1	4 $\pm$ 1
C	11 $\pm$ 3	9 $\pm$ 2	10 $\pm$ 2	11 $\pm$ 2	14 $\pm$ 4	14 $\pm$ 3	11 $\pm$ 2	12 $\pm$ 1	12 $\pm$ 2	12 $\pm$ 2
D	11 $\pm$ 3	10 $\pm$ 2	14 $\pm$ 3	19 $\pm$ 3	21 $\pm$ 3	20 $\pm$ 4	17 $\pm$ 4	11 $\pm$ 2	11 $\pm$ 2	9 $\pm$ 2
Meal only	11 $\pm$ 3	24 $\pm$ 6	35 $\pm$ 3	31 $\pm$ 1	30 $\pm$ 4	30 $\pm$ 4	22 $\pm$ 2	17 $\pm$ 3	13 $\pm$ 3	16 $\pm$ 4
Meal + A	13 $\pm$ 3	31 $\pm$ 4	41 $\pm$ 5	39 $\pm$ 9	25 $\pm$ 5	25 $\pm$ 5	22 $\pm$ 5	18 $\pm$ 3	14 $\pm$ 3	18 $\pm$ 5
Meal + B	5 $\pm$ 1	27 $\pm$ 5	26 $\pm$ 4	18 $\pm$ 2	16 $\pm$ 4	13 $\pm$ 2	10 $\pm$ 2	9 $\pm$ 2	6 $\pm$ 2	5 $\pm$ 2
Meal + C	11 $\pm$ 3	33 $\pm$ 7	40 $\pm$ 4	38 $\pm$ 7	40 $\pm$ 3	45 $\pm$ 9	43 $\pm$ 5	32 $\pm$ 5	22 $\pm$ 6	14 $\pm$ 2
Meal + D	15 $\pm$ 3	35 $\pm$ 8	49 $\pm$ 4	41 $\pm$ 4	41 $\pm$ 5	30 $\pm$ 3	31 $\pm$ 9	30 $\pm$ 6	23 $\pm$ 3	15 $\pm$ 2

TABLE III

Blood glucose levels in seven healthy volunteers following a single oral dose ingested both on an empty stomach and together with a standardized breakfast. A) tolbutamide 500 mg; B) chlorpropamide 250 mg; C) glibenzclamide 5 mg; D) glipizide 5 mg. Statistical significance is indicated in text. Means ($\pm$ SEM) indicated.

	Time after intake of drug and/or meal (min)									
	0	30	45	60	75	90	120	150	180	
A	4.1 ± 0.1	3.9 ± 0.2	3.8 ± 0.1	3.6 ± 0.2	3.6 ± 0.1	3.6 ± 0.2	3.5 ± 0.1	3.4 ± 0.3	3.8 ± 0.1	
B	4.4 ± 0.2	4.6 ± 0.2	4.4 ± 0.1	4.3 ± 0.1	4.2 ± 0.2	4.2 ± 0.1	4.1 ± 0.1	4.2 ± 0.2	4.5 ± 0.2	
C	4.6 ± 0.2	4.2 ± 0.3	4.1 ± 0.2	3.9 ± 0.2	3.6 ± 0.3	3.4 ± 0.2	3.2 ± 0.2	3.3 ± 0.2	3.3 ± 0.2	
D	4.0 ± 0.2	3.8 ± 0.3	3.4 ± 0.2	2.8 ± 0.2	2.3 ± 0.2	2.5 ± 0.2	2.8 ± 0.2	3.0 ± 0.2	3.3 ± 0.1	
Meal only	4.3 ± 0.2	5.5 ± 0.2	5.0 ± 0.4	4.4 ± 0.3	3.8 ± 0.2	3.9 ± 0.2	4.0 ± 0.2	4.1 ± 0.1	4.2 ± 0.1	
Meal + A	4.1 ± 0.1	5.0 ± 0.3	4.4 ± 0.3	3.4 ± 0.2	3.3 ± 0.2	3.1 ± 0.2	3.6 ± 0.2	3.7 ± 0.2	4.0 ± 0.2	
Meal + B	4.6 ± 0.1	4.9 ± 0.4	4.4 ± 0.3	4.1 ± 0.3	3.9 ± 0.2	4.0 ± 0.2	4.3 ± 0.2	4.3 ± 0.1	5.0 ± 0.3	
Meal + C	4.2 ± 0.2	5.9 ± 0.5	4.9 ± 0.6	4.0 ± 0.5	3.3 ± 0.3	3.2 ± 0.3	3.0 ± 0.2	3.2 ± 0.1	3.5 ± 0.1	
Meal + D	4.1 ± 0.1	5.0 ± 0.3	4.0 ± 0.4	2.7 ± 0.5	2.5 ± 0.3	2.8 ± 0.3	2.7 ± 0.1	3.5 ± 0.1	3.3 ± 0.3	

INFLUENCE OF FOOD INTAKE ON THE ABSORPTION AND EFFECT OF GLIPIZIDE
IN DIABETICS AND IN HEALTHY SUBJECTS

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The influence of food intake on the single dose (5 mg) kinetics and effects of glipizide was examined in 9 healthy volunteers and in 14 diabetics, previously not exposed to sulfonylurea. The serum concentrations of glipizide were examined by high-pressure liquid chromatography, plasma insulin concentrations by radioimmunoassay, and blood glucose concentrations by enzymatic methods. The volunteers were examined after intake of glipizide both in the fasting state and together with a standardized breakfast of 1800 kJ, while the patients were examined after intake of glipizide together with, and 30 min before, the standardized breakfast. In addition, both groups were examined after intake of the breakfast without drug exposure.

In the volunteers, food intake seemed to influence neither the peak concentration, the elimination half-life nor the bioavailability of the drug. However, food intake significantly delayed the absorption of glipizide; the peak concentration occurred about 30 min later ($p < 0.05$ in paired t -test). Glipizide promoted an increase in plasma insulin and a reduction of blood glucose both during continued fasting and when the drug was taken together with the meal.

In the patients, glipizide promoted a significant increase of plasma insulin and a significant diminution of the blood glucose increase in response to the meal. At breakfast start, as well as 5, 10, 15, 20, 30 and 45 min thereafter, glipizide concentrations were significantly higher when the drug was taken 30 min before, than when ingested concurrently with, the meal. With the former treatment, the increase of plasma insulin occurred earlier and the blood glucose reduction was pronouncedly greater than with the latter treatment.

In conclusion, concurrent intake of food may delay the absorption of glipizide. This helps to explain why administration of glipizide 30 min before breakfast yields a more appropriate relation between the blood concentration of glipizide and the metabolic impact of the meal, promoting a more optimal insulin release and a better glucose disposition than following concurrent intake of drug and meal.

Key words: glipizide; absorption; pharmacokinetics; pharmacodynamics; food intake; blood glucose; plasma insulin.

Food intake has been found to exert an influence on the bioavailability of several drugs (1). Thus, hydralazine (2), propranolol, metoprolol (3), canrenone (4), phenytoin (5), dicoumarol (6), carbamazepine (7), hydrochlorothiazide (8), nitrofurantoin (9) and erythromycin stearate (10) have displayed an enhanced bioavailability when taken together with food, whereas that of isoniazid (11), rifampicin (12), ampicillin (13), and atenolol (14) is reduced.

As appropriate diet regulation is a major factor in the control of diabetes, the relation between food intake and administration of oral antidiabetic drugs should be of particular importance. As far as tolbutamide, chlorpropamide and glibenclamide are concerned, no significant influence on drug bioavailability has been recorded (15, 16). Nevertheless, the effects of these drugs may be dependent upon the timing between intake of drug and food (15, 16). In addition, a recent study (17) has shown that the blood glucose reducing effect of glipizide, a novel, rapid-acting and potent sulfonylurea, is more pronounced if the drug is taken 30 min before, than when taken together with, a meal. The present study deals with the influence of food intake on the kinetics and effect of glipizide in both healthy subjects and diabetics.

MATERIAL AND METHODS

Healthy volunteers

Nine male volunteers served as test subjects. They were all healthy, according to clinical examination and routine blood tests. Their mean ($\pm$ SD) ages and per cent ideal body weights were 26 ($\pm$ 1.9) years (range 23 - 28) and 94.1 ($\pm$ 5.9) per cent (range 85.6 - 102.8). Each subject was extensively informed and gave written consent.

After overnight fasting (10 p.m. to 8 a.m.), each subject came to the laboratory on three different mornings, with intervals of at least one week. They were then given a) a standardized meal alone, b) 5 mg glipizide together with the meal, and c) 5 mg glipizide alone. The drug was given as single 5 mg tablets, all of the same brand and batch (Min(i)diab^(R), Carlo Erba, Milano, Italy). The meal consisted of 400 ml low-fat milk, two slices (20 g) of white bread with 5 g butter, 35 g cheese, and 150 ml non-sweetened black coffee; altogether yielding 1800 kJ (430 kcal). Apart from the meal, no food or liquid

was allowed until 4 h after initiation of the experiment. Thus, when only glipizide was given, the subjects fasted for 4 h in addition to the preceding 10 h (overnight) fasting period.

Diabetic patients

Initially, 11 male and 4 female subjects with maturity-onset diabetes mellitus were included in the study.* In one of the males, glipizide concentrations in serum could not be measured due to interfering substances. Hence, this subject was excluded from the study.

The remaining 14 subjects had a diabetes duration of 0.5 - 4 years. Their mean ages and per cent ideal body weights were 56.8 ($\pm$ 10.9) years (range 27 - 70), and 120.3 ($\pm$ 13.4) per cent (range 95.3 - 145.7). They were regular attenders at the Medical Clinic, Lund University Hospital. None had detectable renal, hepatic or endocrine disease apart from diabetes. All had conventional dietary regulation. None of them had received any oral antidiabetic drugs or insulin prior to the study, and none was kept on thiazides or corticosteroids.

Each subject came in the fasting state (10 p.m. - 8 a.m.) to the outpatient clinic at 8 a.m. on three different occasions with intervals of 5 - 10 days, to be studied with respect to the effect of a) a standardized meal as described for the healthy volunteers, b) 5 mg glipizide together with the meal, and c) 5 mg glipizide 30 minutes before the meal. In addition, the kinetics of glipizide were studied during conditions b and c. To avoid effect variations due to changes in the dietary regimens between tests, 7 patients were studied in the order c - a - b and 7 in the reverse order i.e. b - a - c.

Laboratory procedures

Serial blood samples were obtained through an indwelling antebrachial venous polyethylene catheter. In all 14 diabetic patients, blood glucose,

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* The glucose and insulin responses of these 15 patients to 5 mg glipizide given with and before breakfast have been published previously, in Acta Med. Scand. 203:211, 1978. These data are re-published here, by kind permission of the Editor-in-Chief of Acta Med. Scand.

plasma insulin and serum glipizide were determined at regular intervals for 120 min, and in 7 of the 14 also for 180 min after the standard meal. In the healthy volunteers blood sampling continued for 24 hours. The serum concentrations of glipizide were measured by high-pressure liquid chromatography (18).

In patients, blood glucose concentrations were measured by the glucose oxidase method (19) with a minor modification (20). In volunteers, the hexokinase method (21) was employed. Plasma insulin was analysed by a commercial solid phase radioimmunoassay (Phadebas Insulin-Test^(R), Pharmacia, Uppsala, Sweden).

Calculations

The concentrations of serum glipizide were plotted against time. Peak concentration ($C_{\max}$) was defined as the maximum value recorded. The drug elimination half-lives in volunteers were calculated by regression analyses, and the areas under the glipizide concentration curve (AUC) values (from 0 to 8 h) were estimated by the trapezoidal rule. There was a tendency toward a shift in the half-life after 6 h, and the 24 h concentrations were sometimes too low to permit accurate glipizide measurements. Hence, residual AUC (8 $\rightarrow$ ∞) could not be safely calculated.

Statistics

Statistical calculations were carried out by Student's paired t-tests. Standard deviations are given in brackets.

RESULTS

Healthy volunteers

The serum concentrations of glipizide following ingestion of 5 mg during fasting and non-fasting conditions in the volunteers are shown in Fig. 1, and the kinetic estimates are given in Table I. It appears that food intake influenced neither the peak concentrations, elimination half-lives nor the AUC values. However, the time to reach peak concentrations was prolonged by approximately 30 minutes in the non-fasting state ($p < 0.05$).

Ingestion of the breakfast meal evoked a rapid increase in the plasma concentrations of insulin (Fig. 2, lower panel). When glipizide was added to the meal, significantly higher concentrations were reached at 60, 120 ($p < 0.05$) and 150 ($p < 0.01$) minutes (Fig. 2, lower panel). After administration of glipizide during continued fasting, a significant increase of plasma insulin was noted at 60 ($p < 0.05$), 75 ($p < 0.01$) and 90 ($p < 0.05$) minutes as compared to the initial level (Fig. 2, lower panel).

Ingestion of the meal promoted a rapid increase in blood glucose concentrations (Fig. 2, upper panel). When glipizide was added to the meal, this blood glucose increase was significantly reduced at 45 ($p < 0.01$), 60 ($p < 0.05$), 75, 90 ($p < 0.01$), 120, 150 ($p < 0.001$) and 180 ($p < 0.01$) minutes (Fig. 2, upper panel). When the drug was given during continued fasting, blood glucose concentrations were significantly ($p < 0.001$) reduced from 45 to 180 minutes as compared to the initial level (4.1 ± 0.1 mmol/l). A nadir of $2.2 (\pm 0.2)$ mmol/l was reached at 75 minutes (Fig. 2, upper panel).

Diabetic patients

The serum concentrations of glipizide in the patients are shown in Fig. 3. It can be seen that, when the drug was given 30 minutes before the breakfast meal, glipizide concentrations were significantly greater not only at breakfast start (0 min) but also 5 ($p < 0.01$), 10, 15, 20, 30 ($p < 0.001$) and 45 ($p < 0.01$) min thereafter, as compared to the situation when the tablet was ingested together with the meal.

Ingestion of the breakfast meal without the drug promoted an increase of plasma insulin from an initial mean value of 17 to a peak of 48 mIU/l (Fig. 4, lower panel). When glipizide was added to the meal, significantly higher insulin concentrations were reached at 15, 20 ($p < 0.05$), 45 ($p < 0.01$), 60 ($p < 0.05$), 90 and 120 ($p < 0.01$) minutes (Fig. 4, lower panel). When the drug was given 30 minutes before the meal, the plasma insulin increase occurred earlier than seen during concurrent administration of drug and meal; the former treatment gave significantly higher insulin concentrations when the meal was begun ($p < 0.05$) and 5 ($p < 0.01$) and 10 ($p < 0.001$) minutes after the meal (Fig. 4, lower panel).

The mean fasting blood glucose levels were not significantly different at the three examinations. Ingestion of the meal without the drug evoked a pronounced increase and a slow subsequent decline in blood glucose levels (Fig. 4, upper panel). When glipizide was given together with the meal, the blood glucose concentration was significantly lower at 60 ($p < 0.01$) and 90 - 180 ($p < 0.001$) minutes than when only the meal was given, and the mean glucose concentration returned to the baseline level within 90 minutes as compared to 150 minutes when the drug was not given (Fig. 4, upper panel). When glipizide was given 30 minutes before the meal, the blood glucose increase in response to the meal was significantly reduced as compared to meal only already within 45 minutes ($p < 0.01$) and at all observation times until 180 minutes ($p < 0.001$) (Fig. 4, upper panel). The difference recorded between preprandial and prandial administration of the drug was significant at 90 ($p < 0.01$) and 120 ($p < 0.05$) minutes. In addition, the decremental area, *i.e.* the blood glucose area below baseline, was significantly greater when glipizide was given before than when given together with the meal ($p < 0.05$).

DISCUSSION

In healthy volunteers, the peak concentration of glipizide showed a range of 154 - 356 nmol/l; the range of the time to reach peak concentration varied from $1\frac{1}{2}$ - $2\frac{1}{2}$ hours in the fasting state and $1\frac{1}{2}$ - 4 hours in the non-fasting state, and the AUC variation was about 3-fold. The most pronounced variation was seen in the elimination half-life, which varied from $2\frac{1}{2}$ to more than 6 hours. Previous studies, based on measurements of radiolabelled glipizide have reported half-lives of about 2 hours, but a figure of 6 hours has also been presented (22). Ongoing studies in patients indicate that the elimination half-life variation may be even greater. As samples were not obtained beyond 2 - 3 hours in the patients of the current study, no half-lives were calculated in these subjects. The patients displayed a great variation in absorption.

In the volunteers, food intake did not measurably influence the peak concentrations, the elimination half-lives or the AUC values; however, food intake significantly prolonged the time to reach peak concentration by approximately 30 minutes. In vitro data (23) indicate that

glipizide is poorly dissolved in simulated gastric fluid but is very rapidly dissolved in simulated enteric fluid. Accordingly, it is reasonable to assume that food intake delays glipizide absorption by reducing the rate of gastric emptying.

As verified by the present findings, a single dose of 5 mg glipizide is capable of promoting a considerable increase in insulin release. In order to promote an optimal insulin release, however, glipizide plasma concentration should have reached an effective level already when the meal enters the gastrointestinal tract. This should suffice as a rationale to administer glipizide in due time before, rather than together with, the meal. The recorded food-induced delay in glipizide absorption provides an additional argument in favour of this mode of administration. This is further emphasized by the findings in the patients. Assuming that the effective level is 100 - 200 nmol/l, this was reached within 5 - 10 minutes after breakfast start when the drug had been given half an hour before the meal, but similar levels were not reached until 30 - 45 minutes after breakfast start when the drug had been given together with the meal. As previously reported (17), the preprandial administration was associated with an earlier insulin appearance and an improved disposition of blood glucose (data re-published in the present report).

In conclusion, concurrent intake of food may delay the absorption of glipizide. This helps to explain why administration of glipizide half an hour before the meal promotes a more appropriate relation between the plasma concentration of glipizide and the metabolic impact of the meal, thus yielding a more optimal insulin release and a better glucose disposition than following concurrent intake of drug and meal.

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REFERENCES

1. Melander, A.: Influence of food on the bioavailability of drugs. *Clin. Pharmacokinet.* 3, 337-351 (1978).
2. Melander, A., Danielson, K., Hanson, A., Rudell, B., Scherstén, B., Thulin, T., Wåhlin, E.: Enhancement of hydralazine bioavailability by concomitant intake of food. *Clin. Pharmacol. Ther.* 22, 104-107 (1977).
3. Melander, A., Danielson, K., Scherstén, B., Wåhlin, E.: Enhancement of the bioavailability of propranolol and metoprolol by food. *Clin. Pharmacol. Ther.* 22, 108-112 (1977).
4. Melander, A., Danielson, K., Scherstén, B., Thulin, T., Wåhlin, E.: Enhancement by food of canrenone bioavailability from spironolactone. *Clin. Pharmacol. Ther.* 22, 100-103 (1977).
5. Melander, A., Brante, G., Johansson, Ö., Lindberg, T., Wåhlin-Boll E.: Influence of food intake on the absorption of phenytoin. *Eur. J. Clin. Pharmacol.* 15, 269-274 (1979).
6. Melander, A., Wåhlin, E.: Enhancement of dicoumarol bioavailability by concomitant food intake. *Eur. J. Clin. Pharmacol.* 14, 441-444 (1978).
7. Levy, R.H., Pitlick, W.H., Troupin, A.S., Green, J.R., Neal, J.M.: Pharmacokinetics of carbamazepine in normal man. *Clin. Pharmacol. Ther.* 17, 657-668 (1975).
8. Beermann, B., Groschinsky-Grind, M.: Gastrointestinal absorption of hydrochlorothiazide enhanced by concomitant intake of food. *Eur. J. Clin. Pharmacol.* 13, 125-128 (1978).
9. Bates, T.R., Sequeira, J.A., Tembo, A.V.: Effect of food on nitrofurantoin absorption. *Clin. Pharmacol. Ther.* 16, 63-68 (1974).
10. Malmberg, A.-S.: Absorption of erythromycin stearate after oral administration. *Curr. Med. Res. Opin.* 5, (suppl. 2), 15-18 (1978).
11. Melander, A., Danielson, K., Hanson, A., Jansson, L., Rerup, C., Scherstén, B., Thulin, T., Wåhlin, E.: Reduction of isoniazid bioavailability in normal men by concomitant intake of food. *Acta Med. Scand.* 200, 93-97 (1976).
12. Acocella, G.: Clinical pharmacokinetics of rifampicin. *Clin. Pharmacokinet.* 3, 108-127 (1978).
13. Welling, P.G.: How food and fluid effect drug absorption. *Postgrad. Med.* 62, 75-82 (1977).

14. Melander, A., Stenberg, P., Liedholm, H., Scherstén, B., Wählin-Boll, E.: Food-induced reduction in bioavailability of atenolol. *Eur. J. Clin. Pharmacol.* 16, 327-330 (1979).
15. Sartor, G., Melander, A., Scherstén, B., Wählin-Boll, E.: Influence of food and of age on the single-dose kinetics and effects of tolbutamide and chlorpropamide. *Eur. J. Clin. Pharmacol.* (in press), (1980).
16. Sartor, G., Melander, A., Scherstén, B., Wählin-Boll, E.: Serum glibenclamide in diabetic patients, and influence of food on the kinetics and effects of glibenclamide. *Diabetologia* 18, 17-22 (1980).
17. Sartor, G., Scherstén, B., Melander, A.: Effect of glipizide and food intake on the blood levels of glucose and insulin in diabetic patients. *Acta Med. Scand.* 203, 211-214 (1978).
18. Wählin-Boll, E., Melander, A.: High-pressure liquid chromatographic determination of glipizide and some other sulfonylurea drugs in serum. *J. Chromatogr.* 164, 541-546 (1979).
19. Marks, V.: An improved glucose-oxidase method for determining blood, C.S.F. and urine glucose levels. *Clin. Chim. Acta* 4, 395-400 (1959).
20. Scherstén, B.: Clinical evaluation of a rapid enzyme strip method (Dextrostix) for blood glucose estimation. *Acta Med. Scand.* 178, 583-590 (1965).
21. Coburn, H.J., Carrol, J.J.: Improved manual and automated colorimetric determination of serum glucose, with use of hexokinase and glucose-6-phosphate dehydrogenase. *Clin. Chem.* 19, 127-130 (1973).
22. Balante, L., Fabre, J., Zahnd, G.R.: Comparison of the pharmacokinetics of glipizide and glibenclamide in man. *Eur. J. Clin. Pharmacol.* 8, 63-69 (1975).
23. De Santis, A.: Internal report, Istituto Carlo Erba per Ricerche Terapeutiche, Milano, Italy, 1978.

Glipizide

nmol $\times$ l⁻¹

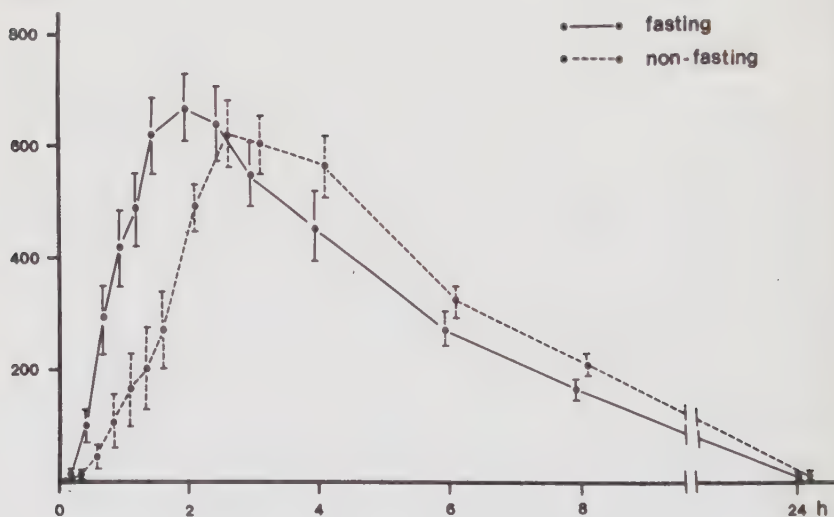


Fig. 1. Serum concentrations (mean + SEM) of glipizide in 9 healthy volunteers following ingestion of 5 mg both in the fasting and in the non-fasting (standardized breakfast) state. The delay of about 30 minutes in the time to reach peak concentration was significant at $p < 0.05$.

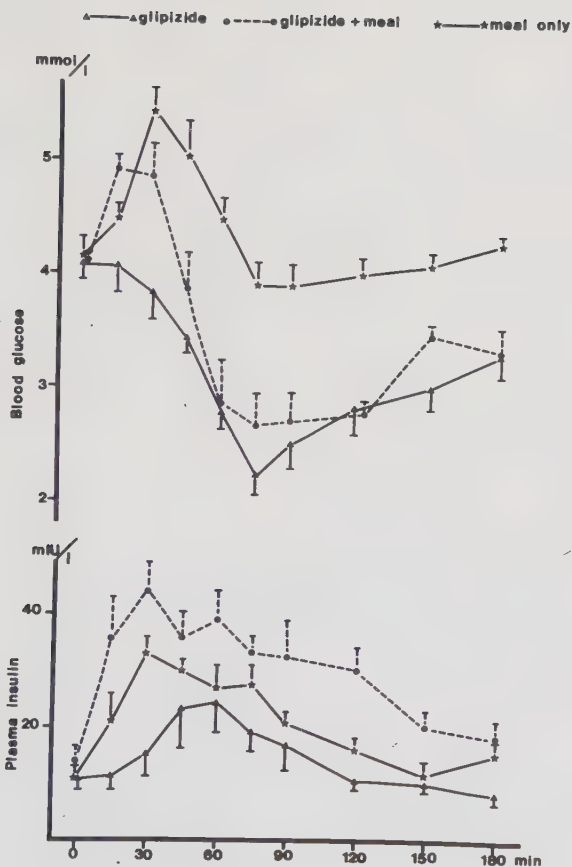


Fig. 2. Plasma insulin (lower panel) and blood glucose (upper panel) concentrations (mean + SEM) in 9 healthy volunteers following administration of standardized breakfast, 5 mg glipizide during continued fasting and 5 mg glipizide taken together with the breakfast.

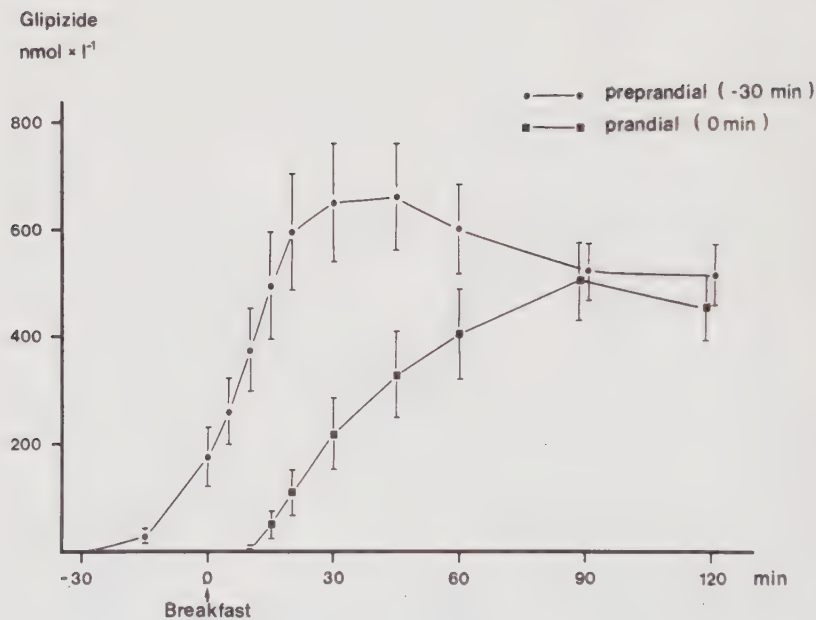


Fig. 3. Serum concentrations (mean + SEM) of glipizide in 14 diabetic patients, previously unexposed to sulfonylurea. The drug (5 mg) was ingested 30 minutes before, as well as concurrently with, a standardized breakfast.

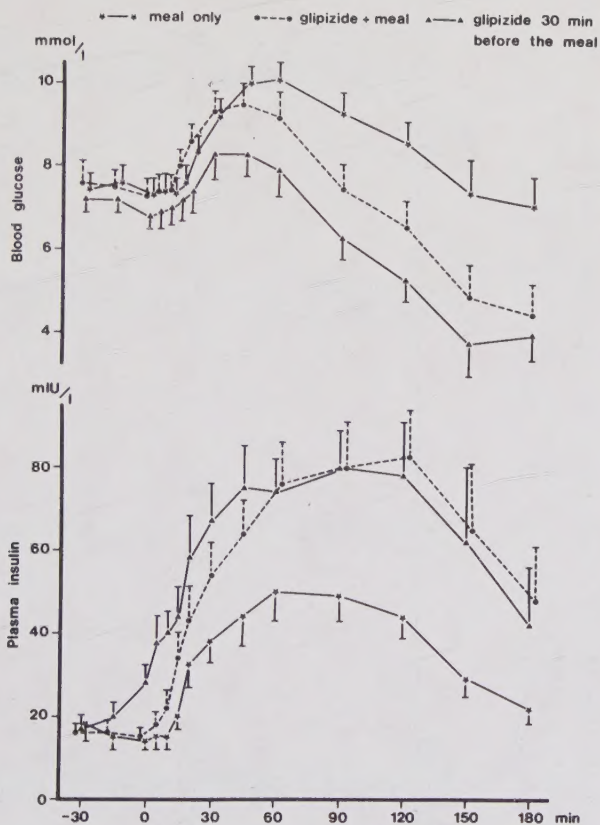


Fig. 4. Plasma insulin (lower panel) and blood glucose (upper panel) concentrations (mean + SEM) in 14 diabetic patients given a standardized breakfast, 5 mg glipizide together with the breakfast, and 5 mg glipizide given 30 minutes before the breakfast. (Data re-published from Acta Med. Scand. by permission of the editor).

TABLE I

Kinetic parameters of glipizide in nine healthy volunteers following a single oral dose (5 mg) both on an empty stomach and together with a standardized breakfast meal. $C_{\max}$ = peak concentration, $t_{\max}$ = time to peak concentration, $t_{1/2}$ = elimination half-life, AUC = area under the serum concentration curve.

Subject No.	$C_{\max}$ (nmol/l)	$t_{\max}$ (h)	$t_{1/2}$ (h)	AUC (0 - 8 h) (nmol x h x l ⁻¹)
1	916	2.5	2.5	4385
2	988	2.0	4.6	4112
3	568	2.5	6.3	2467
4	898	1.5	2.5	3098
5	714	2.0	2.6	2818
6	577	1.5	2.5	2183
7	346	2.0	7.3	1764
8	799	1.5	4.1	3123
9	682	2.5	4.5	3083
Mean $\pm$ SD	720 $\pm$ 204	2.0 $\pm$ 0.4	4.1 $\pm$ 1.8	3004 $\pm$ 844
1	781	2.5	5.2	3307
2	853	4.1	4.8	3086
3	783	1.5	2.4	3019
4	510	2.0	5.7	2859
5	826	2.5	2.0	2930
6	561	2.5	3.8	2422
7	496	2.5	5.4	2560
8	884	3.0	2.3	3343
9	741	3.0	4.2	2684
Mean $\pm$ SD	715 $\pm$ 151	2.6 $\pm$ 0.7	4.0 $\pm$ 1.4	2912 $\pm$ 317

Significance of difference between fasting and non-fasting conditions:

N.S.

 $p < 0.05$

N.S.

N.S.

